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Voltage-Mass Discordance in Suspected Systemic Immunoglobulin Light-Chain (AL) Amyloidosis Mimicking Connective Tissue Disease: A Case Report

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Abstract

Systemic immunoglobulin light-chain (AL) amyloidosis is a potentially life-threatening disorder characterized by extracellular deposition of misfolded immunoglobulin light chains, with cardiac involvement representing a major determinant of prognosis. We describe a 53-year-old man presenting with progressive dyspnea, refractory bilateral lower limb and scrotal edema, and severe orthostatic hypotension. Two months before presentation, he developed gastroesophageal reflux, dysphagia, regurgitation, persistent cough, and fingertip skin thickening and scaling, initially raising suspicion for connective tissue disease, particularly systemic sclerosis. Electrocardiography demonstrated low QRS voltage, while transthoracic echocardiography revealed concentric left ventricular wall thickening (16.3 mm), severely reduced global longitudinal strain (−5%), and relative apical sparing, raising concern for cardiac amyloidosis. NT-proBNP was markedly elevated at 26,382 pg/mL, with troponin of 112 ng/L. Technetium-99m pyrophosphate scintigraphy was negative, although this finding alone could not definitively exclude transthyretin amyloidosis. Serum free light chain testing demonstrated markedly elevated kappa levels (1,087.91 mg/L) and an abnormal kappa/lambda ratio (20.65). Serum immunofixation identified monoclonal IgG kappa gammopathy, while urine immunofixation detected free kappa light chains. Proteinuria was also present, with a creatinine level of 1,34 mg/dl, suggesting possible renal involvement. Collectively, these findings raised strong suspicion for systemic AL amyloidosis with cardiac involvement; however, definitive confirmation by tissue biopsy and amyloid typing was not available. This case highlights the importance of recognizing voltage-mass discordance, relative apical sparing, and multisystem clinical manifestations as diagnostic clues prompting urgent evaluation for cardiac amyloidosis and its underlying etiology.

Categories: Hematology, Cardiology, Cardiac/Thoracic/Vascular Surgery
Keywords: al amyloidosis, cardiac amyloidosis, global longitudinal strain, infiltrative cardiomyopathy, voltage–mass discordance

Introduction

Systemic immunoglobulin light-chain (AL) amyloidosis is a rare but potentially life-threatening disorder characterized by extracellular deposition of misfolded immunoglobulin light chains in multiple organs [1,2]. Cardiac involvement is a major determinant of prognosis and is associated with rapid clinical deterioration and increased mortality, particularly when diagnosis and treatment are delayed [3]. Early recognition remains challenging because of the heterogeneous and frequently nonspecific nature of the initial clinical manifestations.

Patients with AL amyloidosis may present with extracardiac manifestations, including gastrointestinal symptoms, autonomic dysfunction, renal abnormalities, and cutaneous changes, before cardiac involvement is clinically recognized [4,5]. Such manifestations can resemble connective tissue disorders and contribute to diagnostic delays. In particular, progressive fingertip skin thickening accompanied by dysphagia and gastroesophageal reflux may raise suspicion for systemic sclerosis. However, these findings are not disease-specific and require careful evaluation alongside serological, cardiovascular, and other systemic findings.

Cardiac investigations play a pivotal role in identifying suspected infiltrative cardiomyopathy. Increased left ventricular wall thickness on echocardiography, particularly when accompanied by unexpectedly low QRS voltage on electrocardiography, represents voltage-mass discordance, an important clue to cardiac amyloidosis [6]. Speckle-tracking echocardiography may demonstrate markedly impaired global longitudinal strain with relative preservation of apical longitudinal deformation. Although this relative apical sparing pattern supports suspicion for cardiac amyloidosis, it is not pathognomonic and cannot independently establish the diagnosis.

Distinguishing AL amyloidosis from transthyretin (ATTR) amyloidosis is essential because the underlying disease mechanisms, diagnostic pathways, and treatment strategies differ substantially. AL amyloidosis is associated with a monoclonal plasma cell disorder, whereas ATTR amyloidosis results from deposition of

misfolded transthyretin protein. Serum free light chain testing combined with serum and urine immunofixation is essential when evaluating suspected cardiac amyloidosis. Bone-avid tracer scintigraphy, including technetium-99m pyrophosphate imaging, can support the diagnosis of ATTR cardiac amyloidosis under appropriate diagnostic conditions; however, a negative scan does not definitively exclude ATTR amyloidosis. Tissue confirmation and amyloid typing remain important when the diagnosis is uncertain, particularly in the presence of a monoclonal protein.

We present a case of highly suspected systemic AL amyloidosis with cardiac involvement in a 53-year-old man whose initial gastrointestinal symptoms and fingertip skin changes raised concern for connective tissue disease. The subsequent identification of voltage-mass discordance, markedly abnormal myocardial strain, and monoclonal kappa light-chain abnormalities shifted the diagnostic suspicion toward AL amyloidosis. This case highlights the importance of integrating multisystem clinical findings with cardiac imaging and hematologic investigations while recognizing the limitations of noninvasive testing in the absence of definitive tissue confirmation.

Case Presentation

A 53-year-old man presented with progressive exertional dyspnea, refractory bilateral lower limb and scrotal edema, and severe orthostatic hypotension. Two months before admission, he had developed gastroesophageal reflux, dysphagia, postprandial regurgitation, chronic cough, and progressive fingertip skin thickening, raising initial suspicion for a connective tissue disease.

On examination, blood pressure was 82/54 mmHg with a marked postural drop. Jugular venous distension and significant peripheral edema were noted. No Raynaud phenomenon or overt inflammatory joint findings were present.

Electrocardiography demonstrated low QRS voltage in the limb leads (Figure *1*) [6]. Transthoracic echocardiography revealed concentric left ventricular wall thickening (interventricular septum 16.3 mm) with preserved ejection fraction. However, global longitudinal strain was severely reduced (−5.4%) with relative apical sparing (Figure *2*), a pattern highly suggestive of an infiltrative cardiomyopathy [7]. The combination of increased wall thickness and low ECG voltage represented marked voltage-mass discordance, raising strong suspicion for cardiac amyloidosis [6].

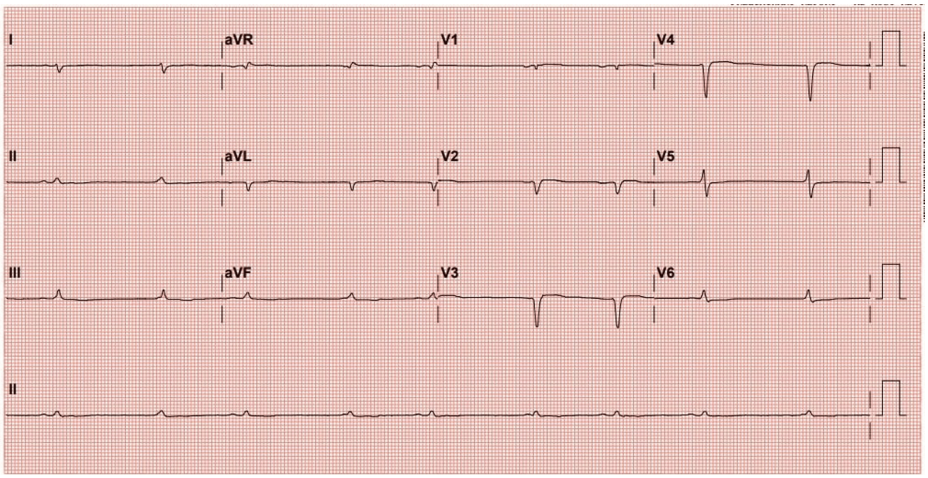


FIGURE 1: Twelve-lead electrocardiogram demonstrating low QRS voltage in the limb leads.

In the setting of increased ventricular wall thickness, this supports voltage–mass discordance suggestive of cardiac amyloidosis.

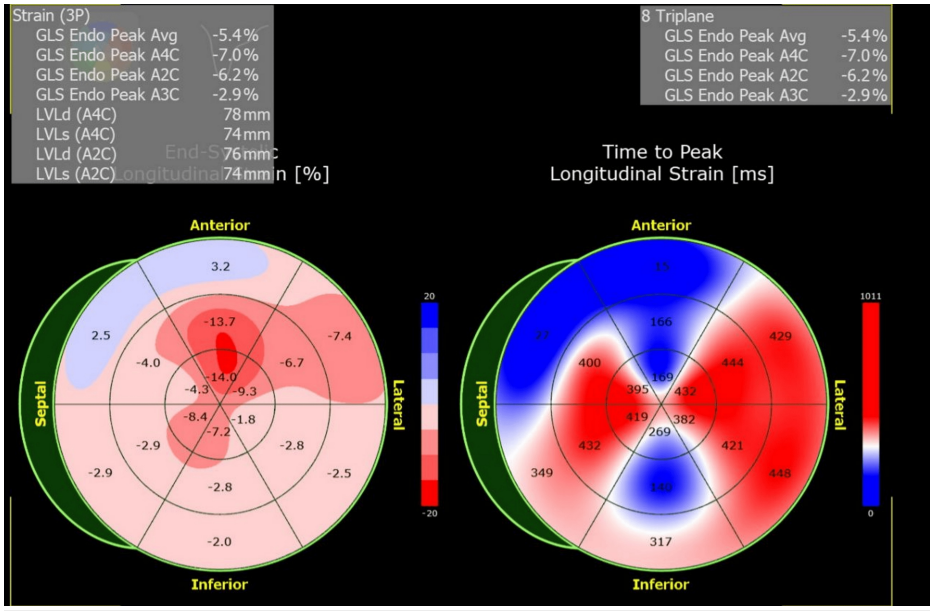


FIGURE 2: Left ventricular global longitudinal strain bull's-eye map demonstrating severely reduced global longitudinal strain (−5.4%) with relative apical sparing.

This pattern is characteristic of cardiac amyloidosis.

Chest radiography demonstrated cardiomegaly with mild pulmonary vascular congestion (Figure 3), consistent with cardiac involvement.

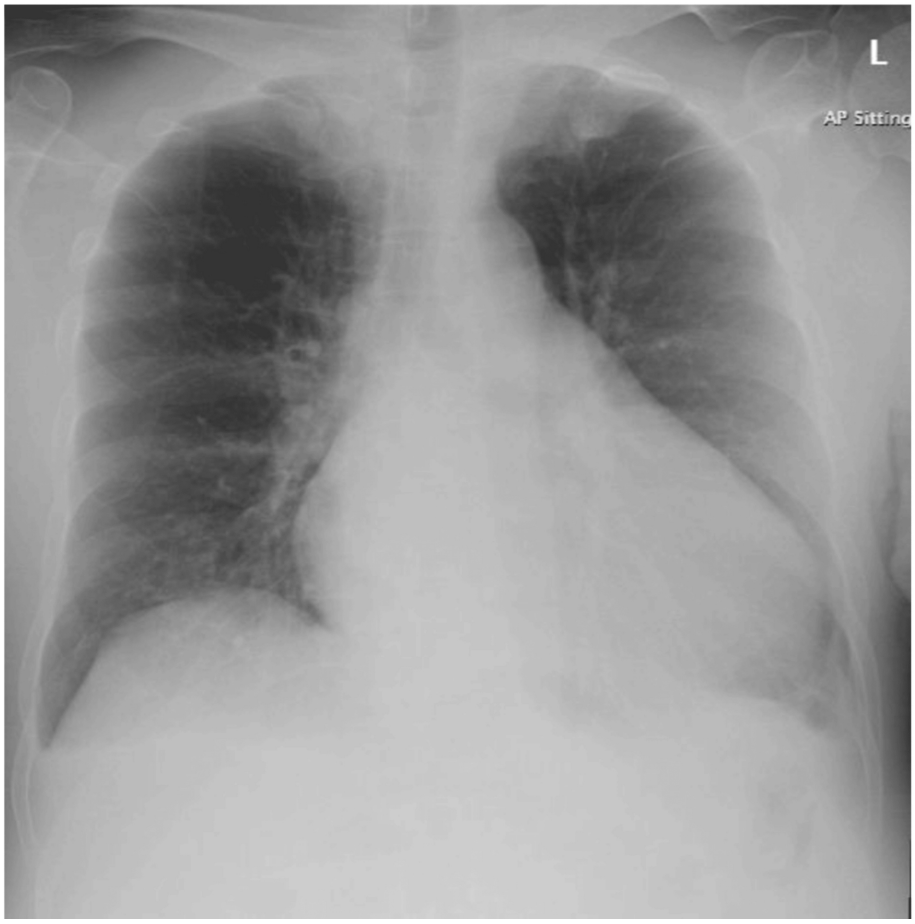


FIGURE 3: Chest radiograph demonstrating cardiomegaly with mild pulmonary vascular congestion.

These findings are consistent with cardiac involvement and heart failure.

Cardiac biomarkers were markedly elevated (NT-proBNP 26,382 pg/mL; troponin 112 ng/L), indicating advanced myocardial involvement [3]. Technetium-99m pyrophosphate scintigraphy demonstrated no significant myocardial tracer uptake (Perugini grade 0) (Figure *4*), arguing against transthyretin amyloidosis [8].

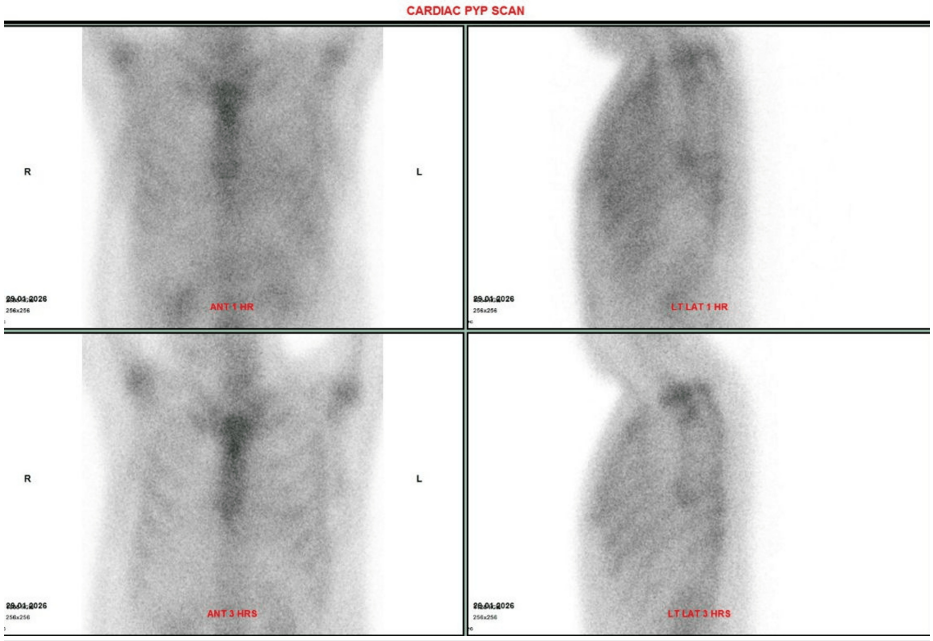


FIGURE 4: Technetium-99m pyrophosphate scan shows no significant myocardial tracer uptake at 1 and 3 hours.

These findings argue against ATTR cardiac amyloidosis.

Serum free light chain testing demonstrated markedly elevated free kappa light chains of 1,087.91 mg/L (reference range: 3.30-19.40 mg/L) and free lambda light chains of 52.69 mg/L (reference range: 5.71-26.30 mg/L), resulting in an abnormal kappa/lambda ratio of 20.65 (reference range: 0.26-1.65). Serum immunofixation identified monoclonal IgG kappa gammopathy, while urine immunofixation detected free kappa light chains (Bence Jones protein). These findings demonstrated a significant monoclonal light-chain abnormality and increased suspicion for AL amyloidosis.

Renal evaluation revealed a serum creatinine increase from 1.17 to 1.36 mg/dL, a urine protein-to-creatinine ratio of 438 mg/g, and approximately 1.0 g of protein excretion on 24-hour urine collection. These abnormalities raised concern for possible renal involvement; however, renal amyloid deposition was not established, and alternative causes of proteinuria and renal dysfunction could not be excluded.

The combination of clinical findings, voltage-mass discordance, markedly abnormal myocardial strain, elevated cardiac biomarkers, and monoclonal kappa light-chain abnormalities raised strong suspicion for systemic AL amyloidosis with cardiac involvement. However, definitive histopathological confirmation and amyloid typing were not available in the reviewed records.

The patient was referred for urgent hematology evaluation to investigate the underlying monoclonal plasma cell disorder and determine the need for tissue biopsy and disease-specific therapy. At the last documented follow-up, the patient had been scheduled for an initial hematology appointment, and plasma cell-directed treatment had not yet been documented. Longitudinal treatment response and clinical outcomes were unavailable.

Discussion

This case highlights the diagnostic complexity of suspected systemic light-chain (AL) amyloidosis, particularly when nonspecific extracardiac manifestations precede recognition of possible cardiac involvement [2]. AL amyloidosis results from the extracellular deposition of misfolded immunoglobulin light chains produced by a clonal plasma cell disorder, potentially leading to progressive multiorgan dysfunction. However, establishing the diagnosis requires histopathological confirmation of amyloid deposition and appropriate amyloid typing.

In this patient, gastrointestinal manifestations, including dysphagia, gastroesophageal reflux, and postprandial regurgitation, accompanied by chronic cough and fingertip skin thickening, initially raised suspicion for connective tissue disease, particularly systemic sclerosis. The negative extractable nuclear antigen (ENA) panel and absence of characteristic clinical features reduced the likelihood of this alternative diagnosis but did not definitively exclude it. Severe orthostatic hypotension additionally raised concern for

possible autonomic dysfunction, while proteinuria suggested potential renal involvement. Although these manifestations may occur in systemic AL amyloidosis, their direct attribution to amyloid deposition could not be established without further organ-specific evaluation [4,5].

The combination of low QRS voltage on electrocardiography and increased left ventricular wall thickness on echocardiography represented a clinically important voltage-mass discordance, raising suspicion for infiltrative cardiomyopathy. Furthermore, markedly reduced global longitudinal strain (−5.4%) with relative apical sparing supported the possibility of cardiac amyloidosis. Although this echocardiographic pattern is a recognized diagnostic clue, it is not pathognomonic and must be interpreted alongside clinical findings, laboratory investigations, and confirmatory testing [6,7].

Technetium-99m pyrophosphate scintigraphy demonstrated no significant myocardial tracer uptake, making transthyretin cardiac amyloidosis less likely. However, a negative PYP scan does not definitively exclude ATTR amyloidosis. These findings highlighted the need for timely hematology assessment and diagnostic confirmation to guide appropriate treatment.

An important limitation of this case was the absence of documented tissue biopsy with amyloid typing and bone marrow evaluation, preventing definitive confirmation of AL amyloidosis and characterization of the underlying plasma cell disorder. Furthermore, the available follow-up was limited, and treatment response and long-term clinical outcomes could not be assessed. These limitations emphasize the distinction between strong clinical suspicion and histopathologically confirmed amyloid disease.

Overall, this case illustrates the importance of integrating electrocardiographic findings, echocardiographic strain imaging, cardiac biomarkers, and monoclonal protein testing when evaluating patients with unexplained ventricular wall thickening and possible multisystem disease. Recognition of voltage-mass discordance and relative apical sparing should prompt targeted evaluation for cardiac amyloidosis, while definitive diagnosis and amyloid typing remain essential for establishing the disease subtype and guiding treatment.

Nevertheless, a negative PYP scan does not definitively exclude ATTR amyloidosis, particularly in early disease or certain ATTR variants. Furthermore, bone-avid tracer scintigraphy cannot establish AL amyloidosis. Definitive differentiation between amyloid subtypes may require tissue biopsy followed by amyloid typing, especially when monoclonal protein studies are abnormal [8].

Serum free light chain analysis demonstrated markedly elevated kappa light chains (1,087.91 mg/L) and an abnormal kappa/lambda ratio of 20.65. Serum immunofixation identified monoclonal IgG kappa gammopathy, while urine immunofixation detected free kappa light chains (Bence Jones protein). These findings strongly supported the presence of an underlying monoclonal plasma cell disorder and increased suspicion for AL amyloidosis. However, monoclonal gammopathy alone does not establish amyloid deposition or confirm the AL subtype. In the absence of documented tissue confirmation and amyloid typing, the diagnosis remained highly suspected rather than definitive.

Renal abnormalities, including a urine protein-to-creatinine ratio of 438 mg/g, approximately 1.0 g of proteinuria on 24-hour urine collection, and a serum creatinine increase from 1.17 to 1.36 mg/dL, raised concern for possible renal involvement. Nevertheless, these findings were nonspecific, and renal amyloidosis could not be confirmed without appropriate further evaluation. The coexistence of cardiac abnormalities and renal findings emphasized the importance of systematic assessment for potential multiorgan involvement.

The markedly elevated NT-proBNP (26,382 pg/mL) and troponin T (112 ng/L) suggested substantial cardiac involvement and an unfavorable prognostic profile if AL amyloidosis were confirmed. Cardiac biomarkers are central to established AL amyloidosis staging systems; however, formal disease staging requires consideration of the specific biomarker assays, relevant thresholds, and the underlying diagnosis [3].

Conclusions

Systemic light-chain (AL) amyloidosis may present with nonspecific gastrointestinal, dermatologic, and autonomic manifestations before cardiac involvement is clinically recognized. This case highlights the diagnostic importance of voltage-mass discordance and severely reduced global longitudinal strain with relative apical sparing in raising suspicion for cardiac amyloidosis. The coexistence of markedly abnormal serum free light chains, monoclonal IgG kappa gammopathy, and elevated cardiac biomarkers further supported a high clinical suspicion for systemic AL amyloidosis. However, these findings are not sufficient for definitive diagnosis without histopathological confirmation and amyloid typing. Early recognition of these clinical and imaging clues should prompt comprehensive monoclonal protein evaluation, timely hematology referral, and appropriate confirmatory investigations. This approach is essential to minimize diagnostic delays and facilitate timely disease-specific management.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mohamed A. Ayoub

Acquisition, analysis, or interpretation of data: Mohamed A. Ayoub

Drafting of the manuscript: Mohamed A. Ayoub

Critical review of the manuscript for important intellectual content: Mohamed A. Ayoub

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Not applicable issued approval Not applicable. This is a single case report. Institutional Review Board (IRB) approval was not required according to institutional policies. Written informed consent was obtained from the patient for publication of this case report and accompanying images. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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